

## General

### Guideline Title

Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update.

### Bibliographic Source(s)

Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K, American Society of Clinical Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013 Jul 1;31(19):2500-10. [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol*. 2006 Jun 20;24(18):1-15.

## Recommendations

### Major Recommendations

#### Clinical Question 1

Are Patients with Cancer Interested in Interventions to Preserve Fertility?

*Recommendation 1.1.* People with cancer are interested in discussing fertility preservation. Health care providers caring for adult and pediatric patients with cancer (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, surgeons, and others) should address the possibility of infertility as early as possible before treatment starts.

What Can Health Care Providers Do to Educate Patients about the Possibility of Reduced Fertility Resulting from Cancer Treatments and to Introduce Them to Methods to Preserve Fertility?

*Recommendation 1.2.* Health care providers should refer patients who express an interest in fertility preservation (and patients who are ambivalent) to reproductive specialists.

*Recommendation 1.3.* Fertility preservation is often possible, but to preserve the full range of options, fertility preservation approaches should be discussed as early as possible, before treatment starts. The discussion can ultimately reduce distress and improve quality of life. Another discussion and/or referral may be necessary when the patient returns for follow-up and if pregnancy is being considered. The discussions should be documented in the medical record.

## Clinical Question 2

What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Males?

*Recommendation 2.1.* Sperm cryopreservation: Sperm cryopreservation is effective, and health care providers should discuss sperm banking with postpubertal males receiving cancer treatment.

*Recommendation 2.2.* Hormonal gonadoprotection: Hormonal therapy in men is not successful in preserving fertility. It is not recommended.

*Recommendation 2.3.* Other methods to preserve male fertility: Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue, should be performed only as part of clinical trials or approved experimental protocols.

*Recommendation 2.4.* Postchemotherapy: Men should be advised of a potentially higher risk of genetic damage in sperm collected after initiation of therapy.

It is strongly recommended that sperm be collected before initiation of treatment because the quality of the sample and sperm DNA integrity may be compromised after a single treatment session. Although sperm counts and quality of sperm may be diminished even before initiation of therapy, and even if there may be a need to initiate chemotherapy quickly such that there may be limited time to obtain optimal numbers of ejaculate specimens, these concerns should not dissuade patients from banking sperm. Intracytoplasmic sperm injection allows the future use of a very limited amount of sperm; thus, even in these compromised scenarios, fertility may still be preserved.

## Clinical Question 3

What Is the Quality of Evidence Supporting Current and Forthcoming Options for Preservation of Fertility in Females?

*Recommendation 3.1.* Embryo cryopreservation: Embryo cryopreservation is an established fertility preservation method, and it has routinely been used for storing surplus embryos after in vitro fertilization.

*Recommendation 3.2.* Cryopreservation of unfertilized oocytes: Cryopreservation of unfertilized oocytes is an option, particularly for patients who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing.

Oocyte cryopreservation should be performed in centers with the necessary expertise. As of October 2012, the American Society for Reproductive Medicine no longer deems this procedure experimental.

More flexible ovarian stimulation protocols for oocyte collection are now available. Timing of this procedure no longer depends on the menstrual cycle in most cases, and stimulation can be initiated with less delay compared with old protocols. Thus, oocyte harvesting for the purpose of oocyte or embryo cryopreservation is now possible on a cycle day-independent schedule.

*Recommendation 3.3.* Ovarian transposition: Ovarian transposition (oophoropexy) can be offered when pelvic irradiation is performed as cancer treatment. However, because of radiation scatter, ovaries are not always protected, and patients should be aware that this technique is not always successful.

Because of the risk of renigration of the ovaries, this procedure should be performed as close to the time of radiation treatment as possible.

*Recommendation 3.4.* Conservative gynecologic surgery: It has been suggested that radical trachelectomy (surgical removal of the uterine cervix) should be restricted to stage IA2 to IB cervical cancer with diameter <2 cm and invasion <10 mm.

In the treatment of other gynecologic malignancies, interventions to spare fertility have generally centered on doing less radical surgery with the intent of sparing the reproductive organs as much as possible. Ovarian cystectomy can be performed for early-stage ovarian cancer.

*Recommendation 3.5.* Ovarian suppression: Currently, there is insufficient evidence regarding the effectiveness of gonadotropin-releasing hormone analog (GnRHa) and other means of ovarian suppression in fertility preservation.

GnRHa should not be relied upon as a fertility preservation method. However, GnRHa may have other medical benefits such as a reduction of vaginal bleeding when patients have low platelet counts as a result of chemotherapy. This benefit must be weighed against other possible risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers. Women interested in this method should participate in clinical trials, because current data do not support it. In a true emergency or rare or extreme circumstances where proven options are not available, providers may consider GnRHa an option, preferably as part of a clinical trial.

*Recommendation 3.6.* Ovarian tissue cryopreservation and transplantation: Ovarian tissue cryopreservation for the purpose of future transplantation does not require ovarian stimulation or sexual maturity and hence may be the only method available in children. It is considered

experimental and should be performed only in centers with the necessary expertise, under institutional review board (IRB)-approved protocols that include follow-up for recurrent cancer.

A theoretic concern with reimplanting ovarian tissue is the potential for reintroducing cancer cells depending on the type and stage of cancer, although so far there have been no reports of cancer recurrence.

*Recommendation 3.7.* Other considerations: Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that fertility preservation interventions (e.g., ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence.

Ovarian stimulation protocols using the aromatase inhibitor letrozole have been developed and may ameliorate this concern. Studies do not indicate increased cancer recurrence risk as a result of subsequent pregnancy.

#### Clinical Question 4

What Is the Role of Health Care Providers in Advising Patients about Fertility Preservation Options?

*Recommendation 4.1.* All oncologic health care providers should be prepared to discuss infertility as a potential risk of therapy. This discussion should take place as soon as possible once a cancer diagnosis is made and before a treatment plan is formulated. There are benefits for patients in discussing fertility information with providers at every step of the cancer journey.

What Should Providers Discuss with Patients about Fertility Preservation?

*Recommendation 4.2.* Encourage patients to participate in registries and clinical studies, as available, to define further the safety and efficacy of these interventions and strategies

*Recommendation 4.3.* Refer patients who express an interest in fertility, as well as those who are ambivalent or uncertain, to reproductive specialists as soon as possible.

*Recommendation 4.4.* Refer patients to psychosocial providers when they are distressed about potential infertility.

#### Special Considerations

Special Considerations: Fertility Preservation in Children

*Recommendation 5.1.* Suggest established methods of fertility preservation (e.g., semen or oocyte cryopreservation) for postpubertal minor children, with patient assent and parent or guardian consent.

For prepubertal minor children, the only fertility preservation options are ovarian and testicular cryopreservation, which are investigational.

## Clinical Algorithm(s)

An algorithm titled "Fertility Preservation Assessment and Discussion Algorithm for Patients with Cancer" is available in the original guideline document.

## Scope

### Disease/Condition(s)

- Fertility/infertility
- Cancer

### Guideline Category

Counseling

Risk Assessment

Treatment

## Clinical Specialty

Hematology

Obstetrics and Gynecology

Oncology

Pediatrics

Radiation Oncology

Surgery

Urology

## Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

## Guideline Objective(s)

To update guidance for health care providers about fertility preservation for adults and children with cancer

## Target Population

All patients of reproductive age (and parents or guardians of children and adolescents) if infertility is a potential risk of therapy

## Interventions and Practices Considered

1. Educating patients with cancer about the possibility of infertility and discussing fertility preservation options with them as early as possible (before treatment starts)
2. Referring patients to reproductive specialists and psychological providers
3. Encouraging patients to participate in registries and clinical studies
4. Male fertility preservation options
  - Sperm cryopreservation
  - Hormonal gonadoprotection (not recommended)
  - Other methods, such as testicular tissue cryopreservation and reimplantation or grafting of human testicular tissue (only as part of clinical trials or approved experimental protocols)
  - Postchemotherapy: advising men of a potentially higher risk of genetic damage in sperm collected after initiation of therapy
5. Female fertility preservation options
  - Embryo cryopreservation

- Cryopreservation of unfertilized oocytes
- Ovarian transposition (oophoropexy)
- Use of conservative gynecologic surgery for gynecologic malignancies
- Gonadotropin-releasing hormone analog (GnRHa) and other means of ovarian suppression in fertility preservation (an option, preferably as part of a clinical trial)
- Ovarian tissue cryopreservation and transplantation
- Ovarian stimulation (letrozole)

## Major Outcomes Considered

- Effects of different anti-tumor agents on sperm production
- Risk of amenorrhea in women treated with modern chemotherapy and radiotherapy
- Success rates for fertility preservation techniques
- Cost of fertility preservation treatment

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

Computerized literature searches of MEDLINE and the Cochrane Collaboration Library were performed. The searches of the English-language literature published from March 1, 2006 to March 1, 2012 combined breast neoplasm terms with fertility preservation and follow-up-related terms and MeSH headings. Results of the databases searches were supplemented with hand searching of the bibliographies of systematic reviews and selected seminal articles, and contributions from Update Committee members' personal files.

Details of the literature search strategy are provided in Data Supplement 3 (see the "Availability of Companion Documents" field). In brief, articles were selected for inclusion in the systematic review of the evidence if they met the following criteria: (1) The study discussed a fertility intervention and reported primary data, and (2) the study population consisted of patients with cancer scheduled for or undergoing cancer treatments that threaten fertility. Articles were excluded from further consideration if they did not report specifically on a fertility intervention and did not report primary data. However, because of the limited nature of the data in many areas, the Update Panel made an a priori decision to also retain high-quality reviews or background articles. A QUOROM diagram that reports the results of the literature search is available in Data Supplement 4 (see the "Availability of Companion Documents" field).

### Number of Source Documents

There were 18 new randomized controlled trials; six systematic reviews, meta-analyses, or previous guidelines; and dozens of narrative reviews, case series and case studies, and editorials.

### Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

### Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Not stated

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

In 2006, the American Society of Clinical Oncology (ASCO) published a clinical practice guideline on fertility preservation for adults and children with cancer. ASCO guidelines are updated periodically by a subset of the original Expert Panel. In October 2012, the Update Panel reviewed the results of a systematic review of the new literature and determined that although the recommendations remained the same (with the exception of adding oocyte cryopreservation as a standard practice, whereas in the previous guideline, it was still considered experimental), some information and tables needed to be updated. In terms of who is responsible for discussing fertility preservation, the original language used by ASCO has been revised: The word "oncologist" was replaced with "health care provider" to include medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons, as well as nurses, social workers, psychologists, and other nonphysician providers.

This clinical practice guideline addresses four overarching clinical questions: (1) Are patients with cancer interested in interventions to preserve fertility? (2) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in males? (3) What is the quality of evidence supporting current and forthcoming options for preservation of fertility in females? (4) What is the role of the oncologist in advising patients about fertility preservation options? Special considerations addressing the fertility needs of children with cancer are also addressed.

The Update Panel included academic and community practitioners, in the fields of adult and pediatric oncology, obstetrics-gynecology, reproductive endocrinology and infertility, health services research, and psychosocial oncology, as well as a patient advocate. The Update Panel completed a review and analysis of evidence (Data Supplements 1 and 2 [see the "Availability of Companion Documents" field]) published between March 2006 and January 2013 to determine whether the recommendations needed to be updated. The Update Panel drafted the guideline manuscript and submitted it for review.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

Internal Peer Review

## Description of Method of Guideline Validation

The American Society of Clinical Oncology Clinical Practice Guideline Committee reviewed and approved the Updated Guideline.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Review of the fertility preservation literature revealed a paucity of large and/or randomized studies. Most data came from cohort studies, case series, small nonrandomized clinical trials, or case reports.

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Appropriate fertility preservation approaches in people undergoing treatment for cancer

### Potential Harms

- Gonadotropin-releasing hormone analog (GnRHa) carries risks such as bone loss, hot flashes, and potential interference with response to chemotherapy in estrogen-sensitive cancers.
- There is a theoretic concern with reimplanting ovarian tissue and the potential for reintroducing cancer cells depending on the type and stage of cancer, although so far there have been no reports of cancer recurrence in humans.
- Because of requirements for scheduling and performing procedures in female patients, some (but not all) interventions may entail a delay in cancer treatment; early referral to a subspecialist can minimize this delay.
- There is a potentially higher risk of genetic damage in sperm collected after initiation of chemotherapy.
- Of special concern in estrogen-sensitive breast and gynecologic malignancies is the possibility that fertility preservation interventions (e.g., ovarian stimulation regimens that increase estrogen levels) and/or subsequent pregnancy may increase the risk of cancer recurrence.

## Qualifying Statements

### Qualifying Statements

- The practice guideline is not intended to substitute for the independent professional judgment of the treating physician. Practice guidelines do not account for individual variation among patients and may not reflect the most recent evidence. This guideline does not recommend any particular product or course of medical treatment. Use of the clinical practice guideline is voluntary.
- Although American Society of Clinical Oncology clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial, ethnic, and socioeconomic disparities in health care contribute significantly to this problem in the United States. Minority racial/ethnic patients with cancer suffer disproportionately from co-morbidities, can experience substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poorer quality care than other Americans. Many other patients lack access to care because they live at a distance from appropriate treatment or reproductive specialty facilities.
- Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest-level fertility preservation advice and treatment to these vulnerable populations. In particular, no patient should be excluded from consideration for discussion of fertility preservation for any reason, including age, prognosis, socioeconomic status, or parity. In discussion, all patients including parents or guardians of children and adolescents should be encouraged to consider fertility preservation, even though there may be financial or insurance barriers. Discussing infertility and introducing the possibility of fertility

preservation leads to improved quality of life and diminished distress in all patient populations.

- Limitations of the literature: Review of the fertility preservation literature revealed a paucity of large and/or randomized studies. Most data came from cohort studies, case series, small nonrandomized clinical trials, or case reports. Fertility preservation methods are still applied relatively infrequently in patients with cancer, limiting greater knowledge about the success and effects of different interventions and the long-term health of offspring. Insufficient attention is paid to the potential positive and negative effects, both physical and psychological, of fertility preservation. There is a need for research about decision making regarding the future use of cryopreserved tissue and posthumous reproduction.

## Implementation of the Guideline

### Description of Implementation Strategy

For information on the American Society for Clinical Oncology (ASCO) implementation strategy, please see the [ASCO Web site](#)

### Implementation Tools

Clinical Algorithm

Patient Resources

Resources

Slide Presentation

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Staying Healthy

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

Loren AW, Mangu PB, Beck LN, Brennan L, Magdalinski AJ, Partridge AH, Quinn G, Wallace WH, Oktay K, American Society of Clinical



## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2006 Jun 20 (revised 2013 Jul 1)

## Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

## Source(s) of Funding

American Society of Clinical Oncology

## Guideline Committee

Fertility Preservation for Patients with Cancer Guideline Update Panel

## Composition of Group That Authored the Guideline

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## Financial Disclosures/Conflicts of Interest

The Update Panel was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflicts of Interest Management Procedures for Clinical Practice Guidelines (Procedures, summarized at <http://www.asco.org/guidelinescoi> ). Members of the Update Panel completed a disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as the result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with the Procedures, the majority of the members of the Update Panel did not disclose any such relationships.

The author(s) indicated no potential conflicts of interest.

## Guideline Status

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This guideline updates a previous version: Lee SJ, Schover LR, Partridge AH, Patrizio P, Wallace WH, Hagerty K, Beck LN, Brennan LV, Oktay K. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. J Clin Oncol. 2006 Jun

## Guideline Availability

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: [guidelines@asco.org](mailto:guidelines@asco.org)

## Availability of Companion Documents

The following are available:

- Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2013. 18 p. Electronic copies: Available in Portable Document Format (PDF) from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .
- Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. Slide set. 2013. 30 p. Electronic copies: Available in PDF  and PowerPoint  from the ASCO Web site.
- ASCO University focus under 40 course. Electronic copies: Available from the [ASCO Web site](#) .
- Discussing fertility preservation with men (video). Available from the [ASCO Web site](#) .
- Discussing fertility preservation with women (video). Available from the [ASCO Web site](#) .

## Patient Resources

The following are available:

- Preserving your fertility before cancer treatment. Patient information. Alexandria (VA): American Society of Clinical Oncology; 2013. 1 p. Electronic copies: Available in Portable Document Format (PDF) from the [Cancer.Net Web site](#) .
- Sexual and reproductive health. Patient information. Electronic copies: Available from the [Cancer.Net Web site](#) .

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## NGC Status

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